

WHAT IS CLAIMED:

1. An isolated altered human inosine monophosphate dehydrogenase (IMPDH) that contains one or more alterations in:
 - (a) the sequence of amino acids from a position corresponding to amino acid 330 to a position corresponding to amino acid 451 of SEQ. ID. NO. 2;
 - (b) the sequence of amino acids from a position corresponding to amino acid 330 to a position corresponding to amino acid 441 of SEQ. ID. NO. 2;
 - 10 (c) the sequence of amino acids from a position corresponding to amino acid 330 to a position corresponding to amino acid 400 of SEQ. ID. NO. 2;
 - (d) the sequence of amino acids from a position corresponding to amino acid 330 to a position corresponding to amino acid 355 of SEQ. 15 ID. NO. 2; or
 - (e) the sequence of amino acids from a position corresponding to amino acid 333 to a position corresponding to amino acid 351 of SEQ. ID. NO. 2;
- 20 whereby the altered IMPDH is resistant to a purine biosynthesis inhibitor.
2. The isolated IMPDH of claim 1, wherein the purine biosynthesis inhibitor is mycophenolic acid or a derivative, analog or metabolite thereof.
3. The isolated IMPDH of claim 1 containing one or more alterations in the sequence of amino acids from a position corresponding to amino acid 333 to a position corresponding to amino acid 351 of SEQ. 25 ID. NO. 2.
4. The isolated IMPDH of claim 1 containing an amino acid other than threonine at a position corresponding to amino acid 333 of SEQ. ID. NO. 2 or an amino acid other than serine at a position corresponding to amino acid 351 of SEQ. ID. NO. 2 or an amino acid 30

other than threonine at a position corresponding to amino acid 333 of SEQ. ID. NO. 2 and an amino acid other than serine at a position corresponding to amino acid 351 of SEQ. ID. NO. 2.

5. The isolated IMPDH of claim 4, wherein the amino acid other
than threonine at a position corresponding to amino acid 333 is isoleucine
or a conservative substitution thereof and the amino acid other than
serine at a position corresponding to amino acid 351 is tyrosine or a
conservative substitution thereof.

10. The IMPDH of claim 1, comprising the sequence of amino acids set forth in SEQ. ID. NO. 4 or the sequence of amino acids set forth in SEQ. ID. NO. 4 containing an alanine at amino acid 190 and a glycine at amino acid 191.

15. 7. An isolated nucleic acid molecule encoding the IMPDH of claim 1.

8. An isolated nucleic acid molecule encoding the IMPDH of claim 2.

9. An isolated nucleic acid molecule encoding the IMPDH of claim 3.

10. An isolated nucleic acid molecule encoding the IMPDH of
20 claim 6.

Q10.15. → 11. The isolated nucleic acid molecule of claim 10, comprising the sequence of nucleotides 48 to 1589 in SEQ. ID. NO. 3 or the sequence of nucleotides 54-1595 of Figure 1 or the sequence of nucleotides 48 to 1589 in SEQ. ID. NO. 3 containing the sequence of
25 nucleotides TGCAGG at nucleotides 614-619.

12. The isolated nucleic acid molecule of claim 7, wherein the codon for the amino acid at a position corresponding to amino acid 333 of SEQ. ID. NO. 2 encodes an amino acid other than threonine or the codon for the amino acid at a position corresponding to amino acid 351 of SEQ. ID. NO. 2 encodes an amino acid other than serine or the codon for the amino acid at a position corresponding to amino acid 333 of SEQ.

ID. NO. 2 encodes an amino acid other than threonine and the codon for the amino acid at a position corresponding to amino acid 351 of SEQ. ID. NO. 2 encodes an amino acid other than serine.

13. A vector, comprising the nucleic acid molecule of claim 7.
- 5 14. A vector, comprising the nucleic acid molecule of claim 10.
15. A cell, comprising heterologous nucleic acid wherein the heterologous nucleic acid comprises the nucleic acid molecule of claim 7.
16. A cell, comprising heterologous nucleic acid wherein the heterologous nucleic acid comprises the nucleic acid molecule of claim 10.
- 10 17. An isolated cell, comprising nucleic acid wherein the nucleic acid comprises the nucleic acid molecule of claim 10.
18. The cell of claim 15 that is a T-lymphocyte or a B-lymphocyte.
- 15 19. The cell of claim 16 that is a T-lymphocyte or a B-lymphocyte.
20. A non-cancerous human lymphocyte, comprising an altered inosine monophosphate dehydrogenase (IMPDH) that is resistant to a purine biosynthesis inhibitor.
- 20 21. The lymphocyte of claim 20, wherein the purine biosynthesis inhibitor is mycophenolic acid or a derivative, metabolite or analog thereof.
22. The lymphocyte of claim 20, wherein the lymphocyte is a T-lymphocyte or B-lymphocyte.
- 25 23. A method of providing for selective proliferation, viability or proliferation and viability of a first cell relative to a second cell, comprising:
introducing a nucleic acid encoding an altered mammalian enzyme into the first cell; and

exposing the first and second cells to conditions that inhibit the unaltered mammalian enzyme but to which the altered mammalian enzyme is resistant;

5 whereby the first cell exhibits greater proliferation, viability or proliferation and viability relative to the second cell.

24. The method of claim 23, wherein the mammalian enzyme is a human enzyme.

25. The method of claim 23, wherein the first and second cells are eukaryotic cells.

10 26. The method of claim 24, wherein the first and second cells are eukaryotic cells.

27. The method of claim 25, wherein the first and second cells are mammalian cells.

15 28. The method of claim 26, wherein the first and second cells are mammalian cells.

29. The method of claim 27, wherein the first and second cells are human cells.

30. The method of claim 28, wherein the first and second cells are human cells.

20 31. A method of providing for selective proliferation, viability or proliferation and viability of a first cell relative to a second cell, comprising:

introducing a nucleic acid encoding an altered mammalian enzyme of a nucleotide biosynthesis pathway into the first cell; and

25 exposing the first and second cells to conditions that inhibit unaltered mammalian enzyme but to which the altered mammalian enzyme is resistant;

whereby the first cell exhibits greater proliferation, viability or proliferation and viability relative to the second cell.

30 32. The method of claim 31, wherein the mammalian enzyme is an enzyme of a purine nucleotide biosynthesis pathway.

33. The method of claim 32, wherein the mammalian enzyme is a mammalian inosine monophosphate dehydrogenase (IMPDH).

34. The method of claim 33, wherein the enzyme is a human IMPDH.

5 35. The method of claim 33, wherein the IMPDH is selected from the group consisting of an IMPDH type I and an IMPDH type II.

36. The method of claim 33, wherein the IMPDH is an IMPDH type II and the conditions comprise exposure to an inhibitor of IMPDH type II.

10 37. The method of claim 36, wherein the predominant IMPDH isoform expressed in the cells is IMPDH type II.

38. The method of claim 36, wherein the first and/or second cell is selected from the group consisting of lymphocytes, cancer cells, tumor cells, leukemic cells, proliferating cells, and mesangial cells.

15 39. The method of claim 38, wherein the first and/or second cell is a T-lymphocyte or B-lymphocyte.

40. The method of claim 39, wherein the cell or cells are activated prior to exposure to an inhibitor of IMPDH type II.

20 41. The method of claim 39, wherein prior to exposure to an inhibitor of IMPDH type II, the cells are exposed to one or more compositions selected from the group consisting of antigens, antibodies, cytokines, growth factors and mitogens.

42. The method of claim 33, wherein the IMPDH is an IMPDH type I and the conditions comprise exposure to an inhibitor of IMPDH type 25 II.

43. The method of claim 42, wherein the predominant IMPDH isoform expressed in the cells is IMPDH type II.

30 44. The method of claim 33, wherein the IMPDH is an IMPDH type I and the conditions comprise exposure to an inhibitor of IMPDH type I.

45. The method of claim 44, wherein the predominant IMPDH isoform expressed in the cells is IMPDH type I.

46. The method of claim 33, wherein the IMPDH is an IMPDH type I and the conditions comprise exposure to an inhibitor of IMPDH type 5 I and type II or to an inhibitor of IMPDH type I and an inhibitor of IMPDH type II.

47. The method of claim 31, wherein the nucleic acid introduced into the first cell comprises nucleic acid encoding an altered IMPDH type I and nucleic acid encoding an altered IMPDH type II and the conditions 10 comprise exposure to an inhibitor of IMPDH type I and type II or to an inhibitor of IMPDH type I and an inhibitor of IMPDH type II.

48. The method of claim 33, wherein the IMPDH is an IMPDH type II and the conditions comprise exposure to an inhibitor of IMPDH type I.

15 49. The method of claim 48, wherein the predominant IMPDH isoform expressed in the cells is IMPDH type I.

50. The method of claim 33, wherein the conditions comprise exposure to one or more inhibitors of IMPDH and an inhibitor of a purine salvage pathway enzyme.

20 51. The method of claim 33, wherein the conditions comprise exposure to mycophenolic acid or a derivative, analog or metabolite thereof.

52. The method of claim 33, wherein the conditions comprise exposure to mycophenolate mofetil.

25 53. The method of claim 33, further comprising introducing heterologous nucleic acid into the first cell in addition to the nucleic acid encoding an altered inosine monophosphate dehydrogenase enzyme.

54. The method of claim 33, wherein the nucleic acid encoding an altered IMPDH is introduced into the first cell *in vitro*.

30 55. The method of claim 33, wherein the nucleic acid encoding an altered IMPDH is introduced into the first cell *in vivo* in an organism.

56. The method of claim 55, wherein the altered IMPDH is minimally immunogenic in the organism.

57. The method of claim 33, wherein the nucleic acid encoding an altered IMPDH is introduced into the first cell *ex vivo* and further comprising transfer of the first cell containing the nucleic acid encoding an altered IMPDH or its progeny into an organism.

58. The method of claim 57, wherein the altered IMPDH is minimally immunogenic in the organism.

59. The method of claim 56, wherein the organism is a mammal.

10 60. The method of claim 59, wherein the organism is a human.

61. The method of claim 58, wherein the organism is a mammal.

62. The method of claim 61, wherein the organism is a human.

63. The method of claim 33, wherein the conditions additionally do not substantially affect cells that are not similar or identical to the first cell into which the nucleic acid encoding an altered IMPDH is introduced.

64. The method of claim 63, wherein the first cell is exposed to the conditions *in vivo*.

65. The method of claim 33, wherein the nucleic acid encodes the amino acid sequence set forth in SEQ. ID. NO. 32.

20 66. The method of claim 33, wherein the nucleic acid comprises the sequence of nucleotides 67 to 1611 in SEQ. ID. NO. 31.

Scalp 67. The method of claim 33, wherein the nucleic acid encodes the amino acid sequence set forth in SEQ. ID. NO. 30 except that the codon for amino acid 333 encodes an amino acid other than threonine.

25 68. The method of claim 33, wherein the nucleic acid encodes the amino acid sequence set forth in SEQ. ID. NO. 30 except that the codon for amino acid 351 encodes an amino acid other than serine.

69. The method of claim 33, wherein the nucleic acid encodes the amino acid sequence set forth in SEQ. ID. NO. 30 except that the 30 codon for amino acid 333 encodes an amino acid other than threonine

and the codon for amino acid 351 encodes an amino acid other than serine.

70. The method of claim 34, wherein the nucleic acid encodes the amino acid sequence set forth in SEQ. ID. NO. 2 except that the 5 codon for amino acid 333 encodes an amino acid other than threonine.

71. The method of claim 34, wherein the nucleic acid encodes the amino acid sequence set forth in SEQ. ID. NO. 2 except that the codon for amino acid 351 encodes an amino acid other than serine.

72. The method of claim 34, wherein the nucleic acid encodes 10 the amino acid sequence set forth in SEQ. ID. NO. 2 except that the codon for amino acid 333 encodes an amino acid other than threonine and the codon for amino acid 351 encodes an amino acid other than serine.

73. The method of claim 34, wherein the nucleic acid encodes 15 the amino acid sequence set forth in SEQ. ID. NO. 4 or the amino acid sequence set forth in SEQ. ID. NO. 4 containing an alanine at amino acid 190 and a glycine at amino acid 191.

74. The method of claim 34, wherein the nucleic acid comprises the sequence of nucleotides 48 to 1589 in SEQ. ID. NO. 3 or the 20 sequence of nucleotides 48 to 1589 in SEQ. ID. NO. 3 containing the sequence of nucleotides TGCAGG at nucleotides 614-619 or the sequence of nucleotides 54-1595 of Figure 1.

75. The method of claim 34, wherein the nucleic acid encodes the amino acid sequence set forth in SEQ. ID. NO. 2, except that the 25 codon for amino acid 277 encodes an amino acid other than glutamine.

76. The method of claim 34, wherein the nucleic acid encodes the amino acid sequence set forth in SEQ. ID. NO. 2, except that the codon for amino acid 462 encodes an amino acid other than alanine.

77. The method of claim 34, wherein the nucleic acid encodes 30 the amino acid sequence set forth in SEQ. ID. NO. 2, except that the codon for amino acid 277 encodes an amino acid other than glutamine

and the codon for amino acid 462 encodes an amino acid other than alanine.

78. The method of claim 34, wherein the nucleic acid encodes the amino acid sequence set forth in SEQ. ID. NO. 2, except that the 5 codon for amino acid 456 encodes an amino acid other than phenylalanine and the codon for amino acid 470 encodes an amino acid other than aspartic acid.

79. The method of claim 34, wherein the nucleic acid encodes the amino acid sequence set forth in any of SEQ. ID. NO. 6, SEQ. ID. NO. 10, SEQ. ID. NO. 10 and SEQ. ID. NO. 12.

80. The method of claim 34, wherein the nucleic acid comprises the sequence of nucleotides 48 to 1589 in any of SEQ. ID. NO. 5, SEQ. ID. NO. 7, SEQ. ID. NO. 9 and SEQ. ID. NO. 11.

81. The method of claim 33, wherein the first cell is a 15 lymphocyte.

82. The method of claim 34, wherein the first cell is a human T-lymphocyte or B-lymphocyte.

83. The method of claim 32, wherein the mammalian enzyme is selected from the group consisting of ribose phosphate 20 pyrophosphokinase, amidophosphoribosyltransferase, gycinamide ribonucleotide (GAR) synthetase, GAR transformylase, formylglycinamide ribonucleotide (FGAM) synthetase, aminoimidazole ribonucleotide (AIR) synthetase, AIR carboxylase, aminoimidazolesuccinocarboxamide ribonucleotide (SAICAR) synthetase, 25 adenylosuccinate synthase, adenylosuccinate lyase, aminoimidazolecarboxamide ribonucleotide (AICAR) transformylase, inosine monophosphate (IMP) cyclohydrolase and GMP synthase.

84. The method of claim 83, wherein the enzyme is a human 30 enzyme.

85. The method of claim 33, wherein the conditions comprise exposure to one or more compositions selected from the group consisting

of ribavirin, tiazofurin, 5-ethynyl-1- β -D-ribofuranosylimidazole-4-carboxamide, mizoribine, selanazole-4-carboxamide adenine dinucleotide, pyridazines and VX-497.

86. The method of claim 31, wherein the mammalian enzyme is
5 an enzyme of a pyrimidine nucleotide biosynthesis pathway.

87. The method of claim 86, wherein the mammalian enzyme is a mammalian dihydroorotate dehydrogenase (DHODH) enzyme.

88. The method of claim 87, wherein the enzyme is a human DHODH.

10 89. The method of claim 87, wherein the first and/or second cell is selected from the group consisting of lymphocytes, cancer cells, tumor cells, leukemic cells, proliferating cells, and mesangial cells.

90. The method of claim 89, wherein the first and/or second cell is a T-lymphocyte or B-lymphocyte.

15 91. The method of claim 87, wherein the conditions comprise exposure to an inhibitor of DHODH.

92. The method of claim 90, wherein the conditions comprise exposure to an inhibitor of DHODH and the cells are activated prior to exposure to an inhibitor.

20 93. The method of claim 90, wherein the conditions comprise exposure to an inhibitor of DHODH, and, prior to exposure to an inhibitor of DHODH, the cells are exposed to one or more compositions selected from the group consisting of antigens, antibodies, cytokines, growth factors and mitogens.

25 94. The method of claim 87, wherein the conditions comprise exposure to one or more inhibitors of DHODH and an inhibitor of a pyrimidine salvage pathway enzyme.

95. The method of claim 87, wherein the conditions comprise exposure to cinchoninic acid or a derivative, analog or metabolite thereof.

30 96. The method of claim 87, wherein the conditions comprise exposure to one or more compositions selected from the group consisting

of quinolone carboxylic acids, naphthoquinones, isoxazoles, phenoxyquinolines, redoxal and derivatives, analogs or metabolites of any of the foregoing compositions.

97. The method of claim 87, wherein the conditions comprise
5 exposure to one or more compositions selected from the group consisting of 6-fluoro-2-(2'-fluoro-1,1'-biphenyl-4-yl)-3-methyl-4-quinoline carboxylic acid, dichloroally lawsone, lawsone, lapachol, atovaquone, N-(4-trifluoromethylphenyl)-5-methylisoxazol-4-carboxamide and (8-chloro-4-(2-chloro-4-fluoro-phenoxy)quinoline).

10 98. The method of claim 87, further comprising introducing heterologous nucleic acid into the first cell in addition to the nucleic acid encoding an altered DHODH.

99. The method of claim 87, wherein the nucleic acid encoding an altered DHODH is introduced into the first cell *in vitro*.

15 100. The method of claim 87, wherein the nucleic acid encoding an altered DHODH is introduced into the first cell *in vivo* in an organism.

101. The method of claim 100, wherein the altered DHODH is minimally immunogenic in the organism.

102. The method of claim 87, wherein the nucleic acid encoding
20 an altered DHODH is introduced into the first cell *ex vivo* and further comprising transfer of the first cell containing the nucleic acid encoding an altered DHODH or its progeny into an organism.

103. The method of claim 102, wherein the altered DHODH is minimally immunogenic in the organism.

25 104. The method of claim 101, wherein the organism is a mammal.

105. The method of claim 104, wherein the organism is a human.

106. The method of claim 103, wherein the organism is a mammal.

30 107. The method of claim 106, wherein the organism is a human.

108. The method of claim 87, wherein the conditions do not substantially affect cells that are not similar or identical to the first cell into which the nucleic acid encoding an altered DHODH is introduced.

109. The method of claim 108, wherein the first cell is exposed to 5 the conditions *in vivo*.

110. The method of claim 87, wherein the nucleic acid encodes the amino acid sequence set forth in SEQ. ID. NO. 24.

111. The method of claim 87, wherein the nucleic acid comprises the sequence of nucleotides 4 to 1101 in SEQ. ID. NO. 23.

~~10 *al 17* > 112.~~ The method of claim 87, wherein the nucleic acid encodes ~~the amino acid sequence set forth in SEQ. ID. NO. 22 except that the codon for amino acid 26 encodes an amino acid other than histidine.~~

113. The method of claim 87, wherein the nucleic acid encodes the amino acid sequence set forth in SEQ. ID. NO. 20 except that the 15 codon for amino acid 56 encodes an amino acid other than histidine.

114. The method of claim 87, wherein the nucleic acid encodes the amino acid sequence set forth in SEQ. ID. NO. 22 except that the codon for amino acid 105 encodes an amino acid other than valine.

115. The method of claim 114, wherein the codon for amino acid 20 105 encodes a glutamic acid residue.

116. The method of claim 87, wherein the nucleic acid encodes the amino acid sequence set forth in SEQ. ID. NO. 20 except that the codon for amino acid 134 encodes an amino acid other than valine.

117. The method of claim 116, wherein the codon for amino acid 25 134 encodes a glutamic acid residue.

118. A method of providing for selective proliferation, viability or proliferation and viability of a first cell relative to a substantially identical or similar type second cell *in vivo* comprising, introducing a nucleic acid molecule into the first cell; and exposing the first and second cells *in vivo* 30 to conditions that inhibit the proliferation, reduce the viability or inhibit the proliferation and reduce the viability of the substantially identical or

similar type second cell, whereby the first cell exhibits greater proliferation, viability or proliferation and viability relative to the second cell,

wherein:

5 the nucleic acid molecule confers resistance to the conditions on the first cell; and

the conditions primarily directly affect only cells similar to the first cell that do not contain the nucleic acid.

119. The method of claim 118, wherein the nucleic acid encodes 10 the amino acid sequence set forth in SEQ. ID. NO. 4 or the amino acid sequence set forth in SEQ. ID. NO. 4 containing an alanine at amino acid 190 and a glycine at amino acid 191.

SAC → 120. The method of claim 118, wherein the nucleic acid comprises the sequence of nucleotides 48 to 1589 in SEQ. ID. NO. 3 or 15 the sequence of nucleotides 48 to 1589 of SEQ. ID. NO. 3 containing TGCAGG at nucleotides 614-619 or the sequence of nucleotides 54-1595 of Figure 1.

121. The method of claim 118, wherein the nucleic acid encodes the amino acid sequence set forth in any of SEQ. ID. NO. 6, SEQ. ID. NO. 20 8, SEQ. ID. NO. 10 and SEQ. ID. NO. 12.

122. The method of claim 118, wherein the nucleic acid comprises the sequence of nucleotides 48 to 1589 in any of SEQ. ID. NO. 5, SEQ. ID. NO. 7, SEQ. ID. NO. 9 and SEQ. ID. NO. 11.

123. The method of claim 118, wherein the nucleic acid encodes 25 the amino acid sequence set forth in SEQ. ID. NO. 24.

124. The method of claim 118, wherein the nucleic acid comprises the sequence of nucleotides 4-1101 in SEQ. ID. NO. 23.

125. The method of claim 118, wherein the first cell is a T-lymphocyte or B-lymphocyte.

30 126. The method of claim 125, wherein the lymphocyte is a human lymphocyte.

127. The method of claim 118, wherein the condition comprises addition of mycophenolic acid or a derivative, metabolite or analog thereof.

128. The method of claim 118, wherein the condition comprises
5 addition of mycophenolate mofetil.

129. The method of claim 118, further comprising introducing heterologous nucleic acid into the first cell in addition to the nucleic acid molecule that confers resistance to the conditions.

130. The method of claim 118, wherein the nucleic acid molecule
10 that confers resistance to the conditions is introduced into the first cell *in vivo* in an organism.

131. The method of claim 118, wherein the nucleic acid molecule that confers resistance to the conditions is introduced into the first cell *ex vivo* and further comprising transfer of the first cell containing the nucleic
15 acid into an organism.

132. The method of claim 118, wherein the nucleic acid that confers resistance to the conditions encodes a protein that is minimally immunogenic *in vivo*.

133. The method of claim 130, wherein the organism is a
20 mammal.

134. The method of claim 133, wherein the organism is a human.

135. The method of claim 131, wherein the organism is a
mammal.

136. The method of claim 135, wherein the organism is a human.

25 137. A method for transferring a heterologous nucleic acid molecule into an organism, comprising introducing nucleic acids comprising the heterologous nucleic acid molecule and a marker nucleic acid molecule into a first cell in the organism and exposing the organism to conditions that inhibit the proliferation, reduce viability or inhibit
30 proliferation and reduce viability of a substantially identical or similar type cell that does not contain the marker nucleic acid, wherein:

the marker nucleic acid molecule confers resistance to the conditions on the first cell; and

the conditions primarily directly affect only cells similar to the first cell that do not contain the marker nucleic acid.

- 5 138. A method for transferring a heterologous nucleic acid molecule into an organism, comprising introducing nucleic acids comprising the heterologous nucleic acid molecule and a marker nucleic acid molecule into a first cell; introducing the first cell into the organism; and exposing the organism to conditions that inhibit the proliferation,
10 reduce viability or inhibit proliferation and reduce viability of a substantially identical or similar type cell that does not contain the marker nucleic acid, wherein:

the marker nucleic acid molecule confers resistance to the conditions on the first cell; and

- 15 the conditions primarily directly affect only cells similar to the first cell that do not contain the marker nucleic acid.

139. The method of claim 137, wherein the heterologous nucleic acid molecule encodes a therapeutic product.

- 20 140. The method of claim 138, wherein the heterologous nucleic acid molecule encodes a therapeutic product.

141. A method of providing a selective advantage for proliferation of a first cell relative to a second cell, comprising introducing a nucleic acid molecule encoding an altered inosine monophosphate dehydrogenase (IMPDH) into the first cell; wherein

- 25 the altered IMPDH is resistant to an inhibitor of purine biosynthesis; and

the first cell is a mammalian cell.

- 30 142. The method of claim 141, wherein the nucleic acid molecule encodes the sequence of amino acids set forth in SEQ. ID. NO. 4 or the sequence of amino acids set forth in SEQ. ID. NO. 4 containing an alanine at amino acid 190 and a glycine at amino acid 191.

SAC 1 143. The method of claim 141, wherein the nucleic acid molecule comprises the sequence of nucleotides 89 to 1589 in SEQ. ID. NO. 3 or the sequence of nucleotides 48 to 1589 of SEQ. ID. NO. 3 containing TGCAGG at nucleotides 614-619 or the sequence of nucleotides 54-1595 5 of Figure 1.

144. A method of providing a selective advantage for proliferation of a first cell relative to a second cell, comprising introducing a nucleic acid molecule encoding an altered dihydroorotate dehydrogenase (DHODH) into the first cell; wherein

10 the altered DHODH is resistant to an inhibitor of purine biosynthesis; and

the first cell is a mammalian cell.

145. The method of claim 137, wherein the heterologous nucleic acid molecule encodes a product that alters the organism's immune 15 responses and the conditions comprise administering to the organism an immunosuppressive agent.

146. The method of claim 145, wherein the product is an immunomodulatory, anti-inflammatory or protective protein.

147. The method of claim 145, wherein the immunosuppressive 20 agent comprises an inhibitor of one or more enzymes of one or more nucleotide biosynthetic pathways.

148. The method of claim 145, wherein the organism has an immune disorder.

149. The method of claim 145, wherein the first cell is a 25 lymphocyte.

SAC 1 150. The method of claim 137, wherein the heterologous nucleic acid molecule encodes a product that alters the organism's immune responses and the conditions comprise administering to the organism an immunosuppressive agent.

30 151. The method of claim 150, wherein the product is an immunomodulatory, anti-inflammatory or protective protein.

152. The method of claim 150, wherein the immunosuppressive agent comprises an inhibitor of one or more enzymes of one or more nucleotide biosynthetic pathways.

153. The method of claim 150, wherein the organism has an
5 immune disorder.

154. The method of claim 150, wherein the first cell is a lymphocyte.

155. The method of claim 118, wherein the conditions comprise administering to the organism an immunosuppressive agent.

10 156. The method of claim 118, wherein the first cell is a lymphocyte.

157. The method of claim 155, wherein the immunosuppressive agent comprises an inhibitor of one or more enzymes of one or more nucleotide biosynthetic pathways.

15 158. The method of claim 130, wherein the organism has undergone a bone marrow or solid organ transplantation.

Spa 2 159. The method of claim 130, wherein the organism has undergone a bone marrow or solid organ transplantation.

160. A method of providing for selective proliferation, viability or
20 proliferation and viability of a first cell relative to a second cell, comprising:

introducing a nucleic acid encoding a resistant enzyme into the first cell; and

25 exposing the first and second cells to conditions that inhibit a sensitive form of the enzyme but to which the resistant enzyme is resistant;

wherein the second cell contains a sensitive form of the enzyme but does not contain the resistant enzyme; and

30 whereby the first cell exhibits greater proliferation, viability or proliferation and viability relative to the second cell.

161. The method of claim 160, wherein the first and/or second cell is a mammalian cell.

162. The method of claim 161, wherein the resistant enzyme is resistant to an inhibitor of an enzyme of a mammalian nucleotide biosynthesis pathway.

163. The method of claim 162, wherein the resistant enzyme is from a species other than a mammalian species.

164. The method of claim 163, wherein the resistant enzyme is resistant to mycophenolic acid or an analog, derivative or metabolite thereof.

165. The method of claim 164, wherein the resistant enzyme is a *Tritrichomonas foetus* inosine monophosphate dehydrogenase (IMPDH).